UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/163,581	12/07/93	BARBERICH T	SPC8905

EXAMINER
HENLEY III, R

12M2/0225

PHILIP E. HANSEN
HESLIN & ROTHENBERG, P.C.
5 COLUMBIA CIRCLE
ALBANY, NY 12203-5160

ART UNIT	PAPER NUMBER
1205	36

DATE MAILED: 02/25/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 12/7/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-6, 8 and 15-18 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-6, 8 and 15-18 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

CLAIMS 1-6, 8 AND 15-18 ARE PRESENTED FOR EXAMINATION

Applicants' amendment, preliminary remarks and the Information Disclosure Statement filed December 7, 1993 have been received and entered into the application. Accordingly, the specification at page 1 has been amended and as reflected by the attached, completed form PTO-1449, the submitted reference has been considered.

Claims 1-6 and 15-18 remain rejected under 35 U.S.C. § 103 as being unpatentable over Chemical Abstracts 89:123259m (Muittari et al.), already of record, for the reasons of record as maintained in the last Office action dated August 12, 1993.

Applicants' arguments have been carefully considered, but fail to persuade the Examiner of error.

Applicants have averred that the reference does not teach or suggest the use of an optically pure isomer of albuterol either alone or in combination. While the Examiner does agree that an optically pure isomer of albuterol is not highlighted, it cannot be agreed that such an isomer is not suggested by the authors. The individual isomers would have been obvious variants over the corresponding racemate because of their presence in the racemate. It would further have been expected that each isomer would not possess the same efficacy

or side effect profile since the racemate would be expected to exhibit the combined effects of the isomers.

Also, it is argued that the reference teaches to lower the side effects associated with albuterol and thus away from the presently claimed invention because of the adjunctive use of hydroxyzine. Applicants find support for this position in the statement by Muittari et al. that "a combination of salbutamol and hydroxyzine seems, therefore, to be one rational means of treating asthma with fewer side effects than the salbutamol-hydroxyzine-theophylline mixture, but still about the same effectiveness". The Examiner, however, cannot agree and finds this statement to mean that the salbutamol-hydroxyzine combination produced fewer side effects than the salbutamol-hydroxyzine-theophylline combination because in the former, theophylline, a known central nervous system stimulant, was absent.

Applicant further argues that it would have only been obvious to employ one of the isomers of the racemate if it were obvious that one of the isomers provided an advantage over the other. However, as expressed above, it would have been obvious to the skilled artisan that each isomer would not possess the same efficacy or side-effect profile as the other given that the activity exhibited by the racemate would have been recognized as being the result of the additive actions of each isomer.

Applicants also offer at page 5 that "it is worth noting that the mere fact that enantiomers exist does not render the use of a particular enantiomer obvious" (emphasis original). The Examiner cannot concur given the court's finding in In re Adamson et al., 275 F2d 952, 125 USPQ 233 (CCPA 1960) and Brenner et al. v. Ladd, Comr. Pats., 171 F2d 319, 80 USPQ 150 (CCPA 1948) that an optically active isomer is unpatentable over a prior art racemate or optical isomer of opposite rotation in the absence of unexpected or unobvious beneficial properties.

Thus, for these reasons, the claims are deemed to be properly rejected.

Claims 1-5 remain rejected under 35 U.S.C. § 103 as being unpatentable over Brittain et al., Hartley et al. and Buckner et al., each of record, for the reasons of record as maintained in the last Office action in further view of Hawkins et al, also already of record..

Applicants' arguments have been carefully considered, but fail to persuade the Examiner of error in his determination.

Respecting Brittain et al., applicants conclude at page 6 of their remarks that "from a study of the Brittain reference one may conclude nothing definitive regarding either the selectivity or R vs racemic or of the potency of R vs racemic." However, the statement in Brittain at the sentence bridging pages 146-7 that "It was not surprising therefore, to find that (-) salbutamol was much more active than (+) salbutamol." clearly speaks to the contrary.

Respecting Hartley et al., applicants aver that no conclusion can be drawn as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects. However, the skilled artisan would have nevertheless expected the side effect profile of the racemate to be the additive result of the individual isomers and thus he/she would have expected the different isomers to exhibit varying side effect profiles.

As for Buckner et al., applicants point to the fact that the authors concluded that both isomers of albuterol were equally selective for tracheal tissue over atrial tissue and go on to argue that since the authors did not examine racemic albuterol, no conclusion can be drawn as to any potency advantage of a single pure R isomer vs the racemate. However, what appears important here is that from the data presented by Buckner et al., the skilled artisan would have appreciated that (-) salbutamol was effective in relaxing bronchial smooth muscle which clearly supports the Examiner's position that it would have been obvious to do what applicants are claiming.

Respecting Hawkins, the Examiner notes that the authors clearly indicate that the (-) isomer of salbutamol is more active than the (+) isomer and was "significantly" more active than the racemic and that such results are "in agreement with the general finding that a racemic drug's activity lies between those of the two enantiomers"(page 857, column 1, lines 4 and 5 of the text under Fig. 1). Applicants argue that no conclusion can be drawn from this study as to

tissue selectivity. However, such conclusions are clearly provided for by Buckner et al. as discussed above.

Applicants also argues that there are only two situations in which the instantly claimed invention could be found to have been obvious, "(1) a teaching that [R-albuterol] is more than twice as potent as the racemate (which would indicate that the S-isomer's activity is antagonistic to the R-isomer's potency); or (2) a teaching that fewer side effects are associated with the R isomer.". However, for the reasons presented above, the Examiner maintains that there is a third possibility, namely, a teaching of the effectiveness and side effect profile of the racemate which would have led the skilled artisan to expect that the individual isomers possess varying degrees of these properties such that when quantitatively combined would equal the activity of the racemate. Applicants also argue that the prior art is silent as to what the skilled artisan ought to expect. However, it is maintained that the skilled artisan would have expected that a racemic drug's activity lies between those of the two enantiomers as highlighted by Hawkins. Further, applicants offer that one skilled in the art would be, at least, confused by the cited references. However, the results reported by the various authors, while not supportive of the fact that the activities are absolutely predictable, would have nevertheless provided at least a reasonable expectation of successfully employing R-albuterol in the manner claimed. In any event, since it has been established that the racemic mixture and isomeric forms of albuterol have been used or tested as

bronchodilators in the treatment of asthma, the use of compositions containing the claimed isomer in the treatment of asthma is clearly rendered obvious, notwithstanding the inconsistency of the prior art on this point.

It is also noted that applicants argue that a process for the resolution of racemic albuterol would inevitably produce R-albuterol in less than 50% yield which would not have motivated the skilled artisan to prepare and administer this isomer. Such a yield, however, is not seen to be of the determinative importance as urged since it fails to take into account the other factors that would be considered such as the efficacy and safety of the drug.

Applicants further renew their argument based upon the declaration of Gunnar Aberg that there was no teaching in the art that the use of pure R-albuterol enjoyed any advantage in diminution of side effects. However, as previously discussed, the skilled artisan would have expected the activities exhibited by the individual isomers to be components of that exhibited by the racemate and would have expected one isomer to be more or less active than the other. The fact that applicants have identified which of the two isomers produces the least side effects is not seen to be a patentable step.

Claims 6, 8 and 15-18 remain rejected under 35 U.S.C. § 103 as being unpatentable over Brittain et al., Hartley et al., Buckner et al. and Hawkins as

applied to claims 1-5 above in further view of Muittari et al., each of record, for the reasons of record as maintained in the last Office action.

Applicants' argument that Muittari et al. fail to supply a teaching regarding the advantage of the use of the R isomer in diminishing side effects is noted but not deemed persuasive as it would have been expected by one skilled in the art that one of the two entantiomers would possess a different degree of activity from the other.

Respecting the declaration of Dr. Aberg filed July 23, 1993, the Examiner is in agreement with applicants at page 10 of their remarks that the declaration is accepted for what it teaches, namely, "that a person of skill in the art would accept the studies in guinea pig trachea and the experiments of Chapman et al. and Morley et al....as predictive of a higher therapeutic index for R-albuterol.". However, the declaration, as well as newly cited GB 2,255,503 which was published subsequent to applicants' filing date and which shows what applicants are claiming, cannot be afforded the significance urged because such would have been expected by the skilled medical artisan given, for example, the teachings of Hawkins that the (-) isomer of salbutamol is significantly more active than the racemate on guinea pig tracheal tissue.

Finally applicants have averred that the decision *In re Adamson* should not be extended to stand for the proposition that a new method for using an isomer is unpatentable "particularly where, as here, the method unexpectedly provides an

improved therapeutic ratio."(applicants' remarks at page 12). Also, it is argued that applicants' have gone far beyond the evidence of enhanced potency in *Adamson* in showing a reduction of unspecified side effects. However, as previously expressed, it is not seen that an unexpectedly better therapeutic ratio has been demonstrated nor is it considered unobvious that one isomer would be more or less prone to cause side effects.

Thus, for these reasons, the claims are deemed to remain properly rejected.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Henley whose telephone number is (703) 308-4652.

RAYMOND J. HENLEY III
PATENT EXAMINER
GROUP 120 - ART UNIT 125

Henley; rjh
February 24, 1994